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Bartels, Meike

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EDITORIAL

Editorial: The Value of Genetically Informative Designs to Understand Pathways of Intergenerational Transmission and Direction of Causality

Meike Bartels, PhD

One of the greatest challenges in the social, behavioral, and medical sciences is to determine the causality underlying associations between risk factors and behavioral or disease outcomes. An area in which insight into causality, and especially direction of causation of possible risk factors and outcomes, could have enormous (clinical) impact is the field of childhood and adolescent psychiatry. Abundant evidence shows that psychopathology runs in families, but the pathways underlying shared family risk are unclear. Large twin family studies provide robust estimates for the heritability of childhood and adolescent behavioral and emotional problems, but direct non-genetic effects from parent to offspring or vice versa cannot be excluded. Question remains as to whether there is a direct causal effect of parental mental health status on the mental health and well-being of their offspring above and beyond the transmission of genetic susceptibility. Genetically informed methods provide opportunities to tackle this causality challenge.[1]

The study by Ahmadzadeh *et al.*[2] that is the focus of this Editorial includes a systematic review and meta-analysis to investigate whether exposure to parent anxiety is associated with offspring internalizing problems after controlling for genetic relatedness. The paper reflects the important and strengthening position of genetically informative designs in the field of childhood and adolescent mental health and beyond.

The authors start with an informative overview of quasi-experimental genetically informative designs, such as parents with adopted children, parents with children conceived via gamete or embryo donation, identical and nonidentical twin pairs with children, and parents with two or more children who are differentially exposed to the variable of interest. They go on with a meta-analysis to investigate if parent anxiety is associated with offspring internalizing outcomes after accounting for familial genetic confounders.

From an initial 429 records, 8 publications, based on data from 4 population cohorts, were retained, covering the various quasi-experimental designs. Studies were mostly restricted to 1 developmental period and, as for unfortunately most of the studies to date, were based on European ancestry samples. The authors report a negligible and nonsignificant pooled effect size between prenatal anxiety exposure and infant internalizing outcomes ($N_{families}$ >11,700; offspring aged 0.5−10 years, $r = 0.04$, 95% CI = −0.07 to 0.14). However, they show that child exposure to parent anxiety after birth is, after accounting for the effects of genetic transmission, significantly associated with child internalizing problems at the same timepoint ($N_{families}$>12,700; offspring aged 0.75−22 years, $r = 0.13$, 95% CI = 0.04−0.21). Low homogeneity between publications and therefore low statistical power obstructed any test of moderation of this effect by, for example, age, gender, or study design.

Based on the limited number of studies available to test for possible effects of maternal prenatal anxiety symptoms, Ahmadzadeh *et al.*[2] argue that there is a striking need for genetically informative studies across development in more diverse samples. Furthermore, the investigators argue that although they report a significant direct effect from parent anxiety on child internalizing problems, the effect is small and should be interpreted with care. First and foremost, the result is based on cross-sectional data, preventing any claim about the direction of the possible causal path (do parental problems induce offspring problems, or do offspring problems evoke parental problems?) or persistence of the effect over time. The authors continue with a rigorous overview of the role of methodological confounding in the reviewed papers, such as the mix of quasi-experimental designs with their own assumptions and limitations, measurement bias (using 1-item versus multiple-item assessments, external raters, and use of single versus multiple reporter), the

number and combination of observed covariates in each study, and the absence of modeling of assortative mating.

They finish off with avenues for future research, including expanding the analyses beyond the mother–child dyads by taking an extended family approach (such as mothers, fathers, and siblings) and considering within-family and between-family designs to examine the different layers of influences from family composition to cultural and societal factors. They describe the unprecedented opportunities that arise because of the recent progress in genetic epidemiology, especially the increasing number of samples with molecular genetic data resulting in large genotyped datasets, and paint the opportunities for studying intergenerational transmission even in samples that do not contain individuals with known genetic relationships. Last but not least, they strongly emphasize an urgent need for improving diversity, with research in more representative samples, in terms of geographical regions and participant ancestry.

It is especially the accumulating availability of genotyped datasets, as well as the statistical innovations and development of computational tools, that add to a myriad of opportunities to identify the pathways from and to parental and offspring psychopathology. Promising are, for example, polygenic score (PGS) approaches. These approaches revealed the existence of a set of genetic factors influencing a range of traits across the life span with stable associations present throughout childhood.[3] Furthermore, PGS have been shown to be valuable in the development of the genetic nurture approach,[4] where one estimates the effect of sequence variants in the parental genomes that are not transmitted to a child but that affect a child through their impacts on the parents and other relatives. PGS also provide the opportunity for the simultaneous use of parental and offspring polygenic scores to disentangle gene–environment correlation, genetic confounding, and genetic nurture.[5]

Although direct clinical applications of molecular genetic information are not around the corner, embracing the opportunities provided by developments in the field of genetics will pave new ways to improve prevention and intervention strategies for child and adolescent psychiatric problems. Ronald[6] provides an excellent SWAT analysis of polygenic scores for child and adolescent psychiatry and provides an overview of how PRS add to our understanding.[7] A balanced overview of the opportunities and challenges of PRS in psychiatry can also be enjoyed while taking a walk via this excellent podcast starring Professor Cathryn Lewis (https://www.acamh.org/blog/investigating-the-interplay-of-genetics-and-environment-on-development-prof-cathryn-lewis/).

The authors of the study that is the focus of this Editorial also acknowledge that there is a long way to go because of the multi-layer gene–environmental complexity that gives rise to individual differences in parent and offspring psychopathology. Progress and investment in several layers are urgently needed. In an ideal situation, we would have access to large, longitudinal databases with data from multiple raters, in different contexts, and at different ages. Focus should expand beyond the parent–child dyads and include other crucial relationships, such as teacher–child relationships, since gene–environmental correlations and gene–environmental interactions theoretically also take place in school settings. Larger datasets will enable studies in which age and sex are not only considered moderators but are a serious part of the research question and in which stability and change are the focus. Larger datasets enable studying the strong pattern of comorbidity that currently blurs the intergenerational pathways of disease. Although studies in adults have become large enough to conclude that similar genetic variants underlie a number of psychiatric disorders,[8] large homogeneous child and adolescent samples are, although on the rise,[9] still less available. Furthermore, in the ideal situation, we should not limit ourselves to DNA sequence data solely but given, for example, the evidence for the role of DNA methylation,[10] take a multi-omics approach.[11]

In sum, the review and meta-analyses by Ahmadzadeh *et al.*[2] highlights the opportunity for genetically informative designs to inform on direction of causality underlying associations between risk factors and behavioral or disease outcomes. It, however, also stresses an urgent need for new research, with larger multi-omics datasets to identify the pathways underpinning why parental symptoms are associated with the development of offspring problems and beyond. With the evidence to date, clinicians should be careful in drawing firm conclusions about the causal effects of parental mental health on their offspring. It should be acknowledged that effects sizes of all factors (genetic and environmental) are small and add only a little to the overall risk. This calls for a holistic approach that considers the multiple pathway influence of parents' symptoms on children and children's symptoms on their parents.

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Dr. Bartels is with Vrije Universiteit Amsterdam, The Netherlands, and Amsterdam Public Health Research Institute, Amsterdam University Medical Centres, Amsterdam, The Netherlands.

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ORCID: https://orcid.org/0000-0002-9667-7555

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Correspondence to Meike Bartels, PhD, Department of Biological Psychology, Vrije Universiteit, van der Boechorststraat 7-9, Amsterdam, 1081 BT, The Netherlands; e-mail: m.bartels@vu.nl

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